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On the Estimation of Hypoxic Ventilatory Response

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The shape parameter, A, has been used to assess hypoxic sensitivity (ventilatory response, $\dot{V}_E$, to lowered alveolar oxygen tension, P_AO_2) in the model of the form $\dot{V}_E = \dot{V}_{EO} + A/(P_AO_2 - C)$ where C is held constant at 32. In this paper we examine the consequence of holding C constant versus estimating both A and C from the data. Using computer-simulated data from 59 subjects whose A and C values had been previously determined, we indicate that when the actual C value is substantially different from 32, the model with $C = 32$ does not fit the data. In this case, the estimated A value with $C = 32$ is highly dependent upon the lowest value of P_AO_2 obtained in the experimental protocol and can be markedly different from the actual A value. In contrast, when C is also estimated from the subject's data the model fits the data and the estimate of A is unbiased but the precision may be diminished when the actual value of C is low. To improve this precision, we propose a Bayesian estimation scheme that adds a "soft" constraint on C. © 1985 Academic Press, Inc.

INTRODUCTION

Several alternative approaches have been used to assess the ventilatory response to hypoxia (*2, 3, 5, 6, 9, 12*). Of these approaches, the progressive hypoxic test has been most evident in the literature. Since 1970, over fifty studies have utilized the progressive hypoxic test to assess the hypoxic drive in terms of metabolic rate and exercise effects, altitude effects, athletic ability and drug effects.

A problem with the progressive hypoxic test is how best to characterize the response data. If ventilation is related to arterial oxygen saturation, the data can be characterized by the slope and intercept of a linear regression line.

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However, most studies suggest that the stimulus to ventilation during hypoxia is a reduction in arterial O_2 tension rather than O_2 content (*13*). Therefore, ventilation is usually related to alveolar O_2 tension as estimated by end-tidal measurements.

Since this relationship is curvilinear, the problem becomes how best to characterize these stimulus–response data. Although exponential models have been used (*6*), most studies have used a hyperbolic model. The model which has been used most extensively is of the form

$$\dot{V}_E = \dot{V}_{EO} + A/(P_AO_2 - C) \qquad [1]$$

where $\dot{V}_E$ is the observed minute ventilation, $\dot{V}_{EO}$ is the horizontal asymptote ($\dot{V}_E$ at high O_2 tension), A, indicates the shape parameter characterizing the magnitude of the hypoxic sensitivity, P_AO_2 is the alveolar oxygen tension estimated by end-tidal measurements and C is the vertical asymptote (P_AO_2 at high ventilation).

The model form of Eq. [1] was first suggested by Weil *et al.* (*12*) in 1970 although a slightly different form had been used previously by the Oxford group with steady-state studies (*2*). The average value for the parameter C was obtained by "extrapolation" in 18 studies in six normal subjects and determined to be 32. Since that time, numerous studies have been published by several research groups in which the model of Eq. [1] with C held constant at 32 has been used to characterize the hypoxic response. By holding C constant, values for the estimates of A have been compared to one another (*13*).

In contrast to the above approach of holding C constant at 32, for certain kinds of studies it may be more descriptive to estimate the value of both A and C from a subject's data. For example, a recent study in cats (*1*) indicates that an increase in metabolic rate predominantly increases C while elevated CO_2 predominantly increases A. Thus, we would interpret a metabolic rate effect as a right shift of the response curve while a CO_2 effect would be interpreted as an increase in hypoxic sensitivity. Other studies in cats (*11*) suggest that high-altitude blunting of the hypoxic response can be interpreted as a left shift of the response curve. Furthermore, studies in man where C has been estimated from the data suggest a variety of individual C values. In the early sixties, the Oxford group (*2*) determined that $C = 32 \pm 8$ (SD) in 20 normal subjects. Most recently, Ohyabu *et al.* (*7*) determined that there was a wide variation in C in 52 active Judo athletes.

The purpose of the present paper is to examine the consequences of holding C constant at 32 versus estimating both A and C from the data. A computer was used to simulate the hypoxic response data from 59 subjects whose A and C values had been determined as part of a previous study (*7*). Problems with holding C constant versus estimating both A and C are detailed. In addition, we outline methods for obtaining rough estimates of more appropriate A and C values for the studies already published where C has been held constant at 32 and the corresponding estimates for A and $\dot{V}_{EO}$ values have been tabulated.

METHODS

The A and C values for Eq. [1] were determined in 61 Judo athletes as part of a previous study (7). The value of C was determined as that value that yielded the highest correlation coefficient between $\dot{V}_E$ and $1/(P_AO_2 - C)$. With this value of C, the values of A and $\dot{V}_{EO}$ were determined as the slope and intercept for the corresponding linear regression line between $\dot{V}_E$ and $1/(P_AO_2 - C)$.

These A and C values are tabulated in Table 1. Note that out of the 61 subjects, two (subjects 57 and 61) exhibit C values of zero. This means that an optimal correlation coefficient could not be determined for a positive C value, suggesting that the model of Eq. [1] is not appropriate for these particular subjects' data. In the remaining 59 subjects, optimum positive C values were found suggesting an appropriate model fit. The A and C values for these 59 subjects will be used in our computer simulation study.

For each subject, $\dot{V}_E$ computer data were generated for P_AO_2 between 200 and 40 mm Hg at 0.5 mm Hg intervals as long as the $\dot{V}_E$ did not exceed 75 liters/min. When $\dot{V}_E$ exceeded 75 liters/min, the progressive lowering of P_AO_2 was stopped. For comparative purposes, the value of $\dot{V}_{EO}$ was assigned to be 12 liters/min for all subjects. A Gaussian noise source was used to add a typical breath-to-breath variation to the ventilation data. Typical computer simulated data sets are shown in Fig. 1.

As shown in Fig. 1, these data sets can be plotted with C held constant at 32. A linear regression between $\dot{V}_E$ and $1/(P_AO_2 - C)$ yields the slope A_w and the corresponding intercept $\dot{V}_{EO_w}$. These parameter estimates are tabulated in Table 1.

RESULTS

As shown in Fig. 1 for subject 12, when the actual C value is 32, then the linear regression line characterizes the data. However, if C is larger than 32 (subject 7) then the plot of $\dot{V}_E$ versus $1/(P_AO_2 - 32)$ results in a data pattern which is concave upward. Alternatively, if C is less than 32 (subject 59) then the data plot yields a pattern which is concave downward. In both cases the linear regression line does not fit the data.

For cases where a linear regression line is used to characterize curvilinear data, the lowest P_AO_2 point achieved in the experimental protocol highly influences the slope A_w. This point corresponds to the highest $1/(P_AO_2 - 32)$ point. For subject 7, a lower stopping P_AO_2 point implies a higher regression slope, A_w. Alternatively, for subject 59, a lower stopping P_AO_2 point implies a lower regression slope, A_w. For subject 12, A_w is not dependent upon the stopping P_AO_2 point since the actual C value is 32.

Figure 2A indicates a scatter plot between A_w and the actual A value. As shown, the association between A_w and A is rather loose. Moreover, the association between A_w and C is even more scattered (Fig. 2B).

In contrast, Fig. 3A indicates that $\dot{V}_{EO_w}$ is linearly correlated with the actual

TABLE 1

A AND *C* VALUES FOR Eq. [1] AS DETERMINED AS PART OF A PREVIOUS STUDY[a]

Sub. No.	A (liters/min · mm Hg)	C (mm Hg)	$\dot{V}_{EO}$ (liters/min)	A_w (liters/min · mm Hg)	$\dot{V}_{EO_w}$ (liters/min)
1	366	27	12	248	13.3
2	31	30	12	75	11.5
3	226	32	12	226	12.1
4	168	35	12	233	11.3
5	107	36	12	172	11.3
6	438	24	12	249	13.9
7	389	39	12	673	9.2
8	69	38	12	167	10.8
9	563	28	12	409	13.7
10	898	25	12	541	15.6
11	121	31	12	110	12.2
12	234	32	12	234	12.1
13	136	37	12	260	10.5
14	78	33	12	86	12.0
15	112	33	12	123	12.0
16	189	28	12	137	12.6
17	1204	10	12	374	18.9
18	168	26	12	107	12.7
19	75	33	12	82	12.0
20	220	32	12	220	12.1
21	124	36	12	199	11.2
22	582	30	12	490	13.1
23	888	26	12	577	15.1
24	490	27	12	333	13.7
25	362	26	12	231	13.4
26	192	28	12	139	12.6
27	363	22	12	185	13.8
28	84	33	12	92	12.0
29	229	33	12	252	11.8
30	111	33	12	122	12.0
31	234	12	12	78	13.4
32	128	27	12	87	12.5
33	325	26	12	207	13.3
34	94	36	12	151	11.4
35	410	21	12	199	14.0
36	160	26	12	102	12.7
37	34	32	12	34	12.1
38	58	27	12	39	12.3
39	306	24	12	174	13.4
40	33	38	12	79	11.5
41	81	24	12	46	12.4
42	170	41	12	432	9.1
43	296	26	12	189	13.1
44	1138	20	12	528	17.7
45	873	24	12	497	15.7
46	214	41	12	514	8.8

TABLE 1—*Continued*

Sub. No.	A (liters/min · mm Hg)	C (mm Hg)	$\dot{V}_{EO}$ (liters/min)	A_w (liters/min · mm Hg)	$\dot{V}_{EO_w}$ (liters/min)
47	167	33	12	184	11.9
48	250	28	12	182	12.9
49	752	18	12	319	16.0
50	364	18	12	154	14.0
51	343	25	12	206	13.4
52	1130	9	12	339	18.5
53	318	40	12	614	9.0
54	371	34	12	456	11.1
55	732	21	12	356	15.6
56	671	26	12	429	14.5
57	2838	0	12		
58	2000	21	12	1333	16.7
59	783	17	12	318	16.2
60	770	20	12	357	15.9
61	1524	0	12		

[a] Reference (7). $\dot{V}_{EO}$ was set to 12 liters/min for comparative purposes. A_w and $\dot{V}_{EO_w}$ indicate the parameter estimates from the computer simulated data when $C = 32$ (see text).

C value ($r = 0.89$). Furthermore, the percentage change $(A_w - A)/A$ exhibits a tight curvilinear relationship to C (Fig. 3B).

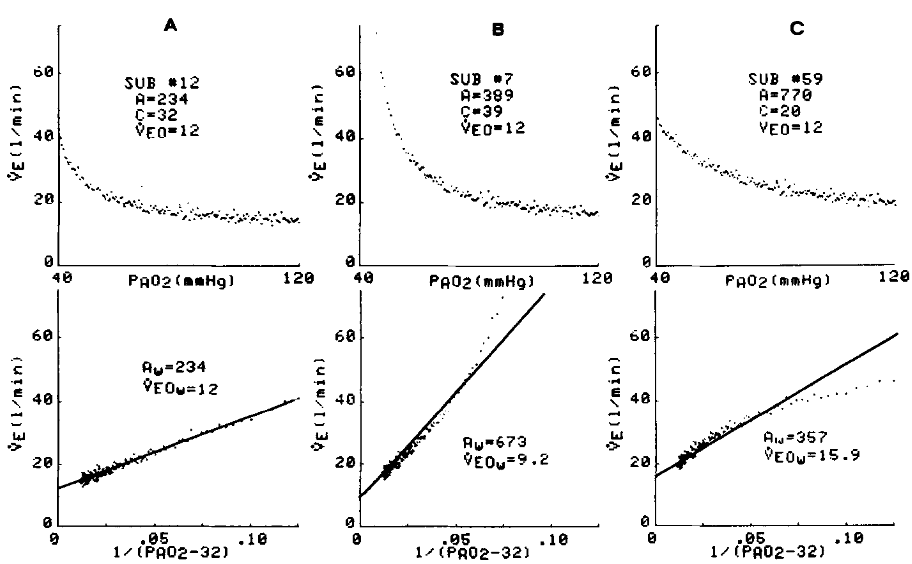

FIG. 1. Computer generated data using the model of Eq. [1] with the A and C values in Table 1. A Gaussian noise source was used to add a typical breath-to-breath variation to the ventilation data. (A) Subject 12 where $C = 32$. (B) Subject 7 where $C = 39$. (C) Subject 59 where $C = 17$.

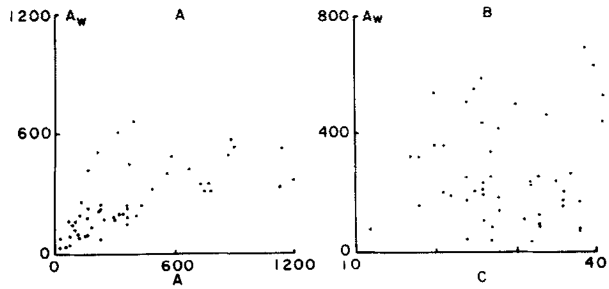

FIG. 2. Scatter plots for the 59 subjects of Table 1. (A) A_w versus A. (B) A_w versus C.

DISCUSSION

Our results suggest that when a subject exhibits a C value substantially different from 32, the regression line $\dot{V}_E$ versus $1/(P_AO_2 - 32)$ does not fit the data (Fig. 1). This means that for these subjects, the A_w value obtained may be markedly different from the actual A value (Fig. 2A). Furthermore, the A_w value actually obtained is highly sensitive to the lowest P_AO_2 point achieved in the experimental protocol (Fig. 1).

There are also problems associated with estimating both A and C from the data. For studies in man, the P_AO_2 cannot be lowered below 40 mm Hg. For particular subjects with low C values and for conditions that tend to shift the curve to the left [e.g., altitude acclimatization (*11*)], the data curvature in the permissible hypoxic range is minimal. The precision for the estimate of C is diminished and this contributes to a variability in the estimate of A.

This concept is illustrated in Fig. 4 for subject 31. One thousand different realizations from the Gaussian noise source have been added to the model. For each realization, the model parameters of Eq. [1] were estimated with C either held constant at 32 or both A and C estimated from the data. These parameter estimates were then combined into histograms as shown in the figure. Note in Fig. 4A where C has been held constant at 32, the distribution for the estimate of A_w is relatively tight (CV = mean/standard deviation = 3.6%) but biased low from the true A value of 234. In contrast, Fig. 4C indicates a broad distribution

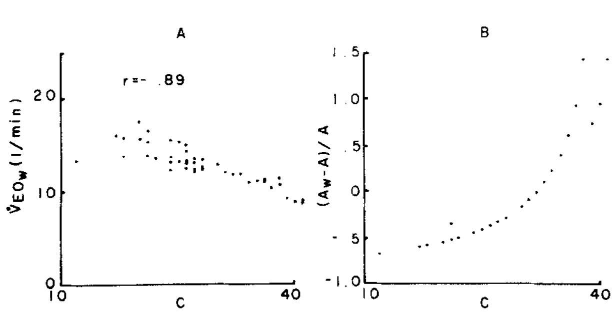

FIG. 3. Relationships among estimated parameters. (A) $\dot{V}_{EO_w}$ is linearly correlated with the actual C value ($r = 0.89$). (B) The percentage change ($A_w - A/A$) exhibits a curvilinear relationship to C. Note all 59 subjects are used but several subject points overlie each other.

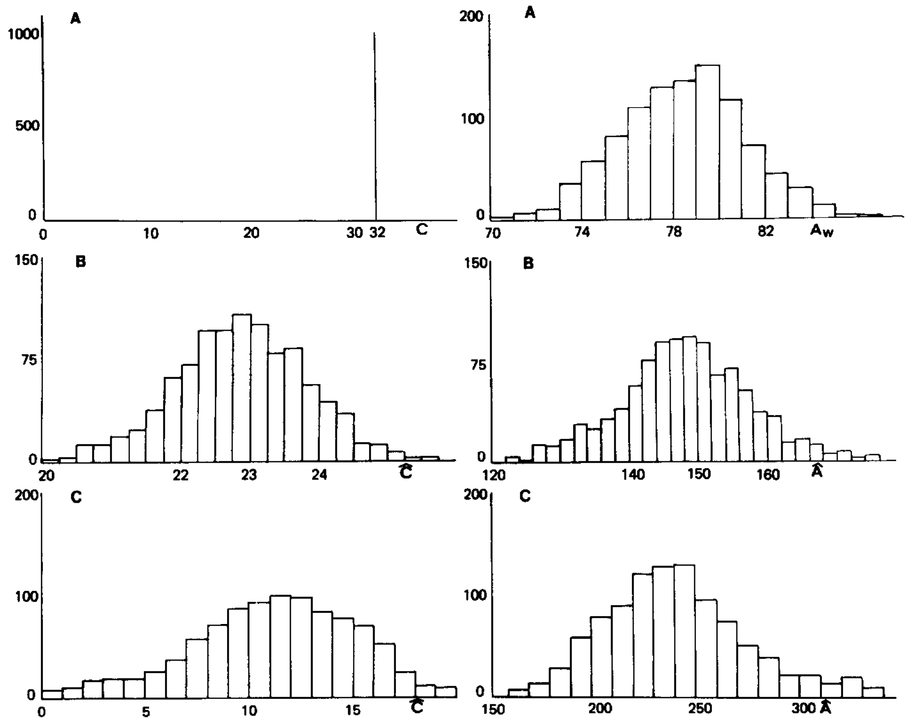

FIG. 4. Histograms of parameter estimates for subject 31. The left-hand axis indicates the frequency of events. (A) C is held constant at 32. (B) Both A and C are estimated with C constrained by a "soft" constraint (Eq. [6], α = 0.005, C_0 = 32). (C) Both A and C are estimated with C unconstrained.

for the estimate of C (CV = 37.7%) and this contributes to the broad distribution for the estimate of A (CV = 14.8%). For high C values this is not the case. Figure 5 indicates the results for subject 7 whose C value is 39. Note in Fig. 5A that when C is held constant at 32, the estimate A_w is biased high from the true A value of 389 with a CV = 0.8%. In contrast to the low C value case (Fig. 4C), when C is estimated from a high C value subject the true value is estimated (Fig. 5B) and thus the distribution for the A value estimate is relatively tight with a CV = 0.8%.

An alternative approach to holding C constant at 32 (hard constraint) or estimating both A and C values (C is unconstrained in the positive range) is to add a "soft" constraint on C based on Bayesian statistics (see below, Eq. [6]). Figure 4B indicates that the "soft" constraint yields a biased estimate of both A and C. However, the variation in the estimate of C is reduced (CV = 4.3%) which yields a reduced variation in the estimate of A (CV = 6.5%). For a high C subject (Fig. 5) this "soft" constraint does not alter the precision or accuracy of the estimate for A and C from that obtained from the unconstrained estimation case. Note that the precision on the estimate for A is similar to that obtained when C is held constant at 32.

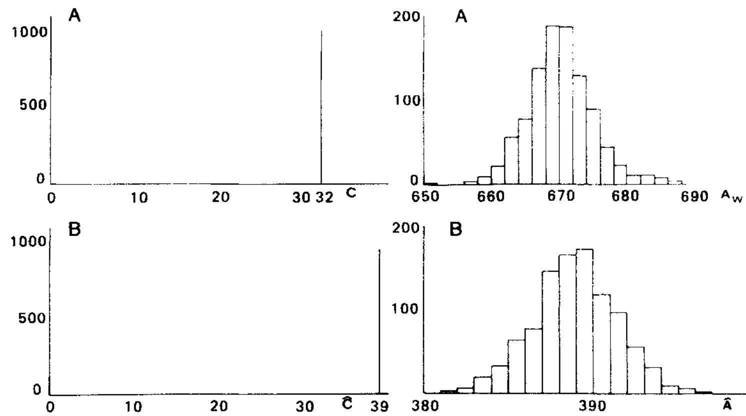

FIG. 5. Histograms of parameter estimates for subject 7. (A) C is held constant at 32. (B) Both A and C are estimated; similar results are obtained with C unconstrained and C constrained by the soft constraint of Eq. [6] ($\alpha = 0.005$, $C_0 = 32$).

The model of Eq. [1] is linear in the parameters A and $\dot{V}_{EO}$ but nonlinear in the parameter C. As suggested by Ohyabu *et al.* (*7*), C can be estimated as that value that yields the highest correlation coefficient between $\dot{V}_E$ on the y axis and $1/(P_AO_2 - C)$ on the x axis. Then, given this value of C, a linear regression line of the form,

$$y = mx + b \qquad [2]$$

yields the slope estimate $\hat{m} = rS_y/S_x$ where r is the correlation coefficient obtained above, S_y is the standard deviation of the y variable (i.e., $\dot{V}_E$) and S_x is the standard deviation of the x variable (i.e., $1/(P_AO_2 - C)$. The intercept estimate is $\hat{b} = \bar{y} - \hat{m}\bar{x}$, where the bar indicates the means value. Thus,

$$\hat{A} = rS_y/S_x \qquad [3]$$

$$\hat{\dot{V}}_{EO} = \bar{y} - rS_y/S_x\bar{x}. \qquad [4]$$

Note that this procedure yields the parameter estimates that minimize the residual mean square error (mse) (*1, 4*). That is, for linear regression the mse is given by

$$\text{mse} = (1 - r^2)S_y^2 \qquad [5]$$

and is minimized by maximizing r, the correlation coefficient. Furthermore, by definition, the slope and intercept estimates given in Eqs. [3] and [4] minimize the mse given in Eq. [5].

An alternative approach to holding C constant at 32 or estimating both A and C unconstrained, is to add a "soft" constraint as motivated by Bayesian statistics (*10*). For this case, Eq. [5] becomes

$$J = (1 - r^2)S_y^2 + \alpha(C - C_0)^2 \qquad [6]$$

where C_0 is an *a priori* estimate of C and α indicates a weighting parameter related to our confidence in C_0 (*10*). If $\alpha = 0$, minimizing J yields the unconstrained estimates of C and A. If α is large, minimizing J yields the estimate of A where C is held constant at C_0. As a compromise, we have set $C_0 = 32$ and $\alpha = 0.005$ for the parameter estimates obtained in Figs. 4 and 5. Using Eq. [6], C can be estimated as that value that minimizes the "cost" function J where r is the correlation coefficient between $\dot{V}_E$ and $1/(P_AO_2 - C)$. This can be accomplished by use of a nonlinear optimization routine or by simply "stepping" through C values until the minimum is found. Then, given this value of C and the corresponding r, the estimates for A and $\dot{V}_{EO}$ are given by Eqs. [3] and [4].

When examining the literature where C has been held constant at 32 and A_w and the corresponding $\dot{V}_{EO_w}$ have been tabulated, it may be possible to obtain a rough estimate of more appropriate A and C values. For example, Table 1 in the original study of Weil *et al.* (*12*), indicates that subject J.V.W. has a $\dot{V}_{EO_w}$ of 2.6 liters/min (average of seven runs). This is substantially below the average of 4.8 liters/min for the 10 subjects. From Fig. 3A in our present study, a low $\dot{V}_{EO_w}$ suggests that a more appropriate C value would be substantially higher than 32. With a higher C value, Fig. 3B indicates a more appropriate A value would be substantially lower than the 217 published in the study of Weil *et al.*

CONCLUSION

There has been a recent effort to update the mathematical and statistical procedures used in the characterization of the CO_2 response slope (*8*). However, little attention has been given to the procedures used in assessing the hypoxic response with the model of Eq. [1]. Because this model is used so extensively in the literature, we have pointed out specific problems with holding C constant at 32 and suggest that both A and C parameter values should be estimated from the data. However, for low C values the precision of the A value estimate is compromised. An alternative approach is to implement a Bayesian scheme that includes a "soft" constraint on C. The ready availability of appropriate computer software and hardware, facilitates the implementation of these estimation procedures as well as other more computer intensive approaches (*8*).

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